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(71) Applicant: **NIPPON SHINYAKU COMPANY, LIMITED**
14, Kisshoin Nishinosho Monguchicho
Minami-ku Kyoto-shi Kyoto 601 (JP)

(72) Inventor: **NAKAMICHI, Kouichi**
13-16, Kitayamadai 1-chome,
Koseicho
Koga-gun, Shiga 520-32 (JP)
Inventor: **IZUMI, Shogo**
3-94, Nishitsutsujigaoka Miyamadai 1-chome
Kameoka-shi, Kyoto 621 (JP)
Inventor: **YASUURA, Hiroyuki**
10-20-312, Hirai 5-chome
Kusatsu-shi, Shiga 525 (JP)

(74) Representative: **Hillier, Peter et al**
Reginald W. Barker & Co.,
Chancery House,
53-64, Chancery Lane
London, WC2A 1QU (GB)

(54) FAST SOLUBLE TABLET.

(57) A tablet which dissolves rapidly in the oral cavity and can be prepared in a simple manner without resort to any special preparation technique. The tablet comprises a sugar alcohol or the like as the principal ingredient and is prepared by the wet granulation method wherein a kneaded mixture of the sugar alcohol or the like with a drug is compression molded before drying. This tablet can be prepared merely by modifying partly the conventional tableting method and has a sufficient physicochemical stability.

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TECHNICAL FIELD

The present invention relates to a drug-containing fast soluble tablet that dissolves rapidly in the oral cavity.

The fast soluble tablet usually dissolves in the oral cavity within 15 seconds to 3 minutes, and is suitable for administration to infants, the aged, severely affected patients and others who have difficulty in taking tablets.

BACKGROUND ART

Oral dosage forms of drugs include tablets, granules, powders and liquids. Liquids, such as syrups, are suitable for administration to the physically weakened aged and infants because they are easily swallowable. However, they are not convenient because they must be accurately weighed for each use. Another drawback is that the tendency to deteriorate easily upon exposure to heat or atmosphere degrades the drug's chemical and physical stability.

Granules and powders are free of the above drawbacks, but they are not easily swallowable, and taking the accurate dose is difficult unless they are taken with water etc.

Tablets are suitable for administration of a certain accurate volumes and offers excellent chemical and physical stability for the drug contained, but they have a drawback of difficult swallow for infants, the aged, severely affected patients and others. Overcoming the drawback of poor swallowability would make it possible to provide an excellent preparation free of the above-described drawbacks in other dosage forms.

As a solution to the problem of poor swallowability in tablets, freeze-dried preparations in a tablet form, based on a water-soluble polymer, have recently been developed (e.g., Japanese Patent Unexamined Publication Nos. 44619/1978 and 86837/1991). They have overcome the drawback of poor swallowability in tablets by causing the preparation to dissolve rapidly in the oral cavity. However, they require a special preparation technology known as freeze-drying, resulting in drawbacks such as difficulty in industrial mass-production, high production cost and poor physical stability.

In recent years, tablets have been produced by subjecting tablet components to compressive shaping under high pressure in a dry state. This is because tablets are essentially intended to be disintegrated in the gastrointestinal tract to cause drug absorption and must be physically and chemically stable from completion of tableting to reach to the gastrointestinal tract, so that the tablet components must be strongly bound together by a compressive pressure. In early times, wet tablets were available, which were molded and shaped into tablets while in a wet state, followed by drying. However, such tablets were not rapidly soluble in the oral cavity because they were intended to be disintegrated in the gastrointestinal tract. Also, as these tablets are not strongly compressed mechanically and lack shape retention, they are not practically applicable to modern use.

DISCLOSURE OF THE INVENTION

The object of the present invention is to provide a fast soluble tablet that can be produced by a simple method without the above-described special preparation technology known as freeze-drying.

Through intensive investigation, the present inventors found that the above object could be accomplished by producing tablets based on a pharmaceutical additive rapidly soluble in water by a modification of the conventional tableting method based on wet granulation and completed the present invention.

A gist of the present invention is characterized by two features:
1) the tablet base component is a pharmaceutical additive rapidly soluble in water, and 2) a kneaded mixture of a drug and a pharmaceutical additive rapidly soluble in water is subjected to compressive shaping while in a wet state.

The present invention is hereinafter described in detail.

The pharmaceutical additive rapidly soluble in water may be any water-soluble crystalline or powdery solid, exemplified by substances in common use as excipients. It is preferable, however, that the pharmaceutical additive is a sweetening substance, since the fast soluble tablet of the present invention dissolves rapidly in the oral cavity. Such substances include succharides such as sucrose, lactose, glucose and fructose, and sugar alcohols such as xylitol, sorbitol and mannitol.

Of the above-mentioned sugar alcohols, xylitol is preferred because it has a good taste and dissolves most rapidly in the oral cavity. Mannitol and lactose are excellent in the compressive property described later, although they are inferior to xylitol in taste and dissolution rate.

In the present invention, these substances may be used in combination. Appropriate combination can offer only a combination of advantages thereof.

The fast soluble tablet relating to the present invention is produced by subjecting a kneaded mixture of a pharmaceutical additive rapidly soluble in water as described above and a drug to compressive shaping before drying when compressive shaping is performed in the conventional tableting method based on wet granulation. The present tablets are different from conventional tablets in that the shaping and drying operations are reversed in order; conventional tablets are produced by mixing starting materials, adding a binder, kneading and drying the mixture and subjecting the mixture to compressive shaping.

The compressive shaping pressure for shaping the fast soluble tablet relating to the present invention may be relatively low, e.g., 50 - 1,000 kg is sufficient. Although decreasing the pressure tends to yield tablets of shorter oral cavity dissolution time, compressive shaping pressures lower than 50 kg result in formation of practically unapplicable tablets with insufficient tensile strength. Although increasing the pressure tends to yield more tough tablets of improved tensile strength, compressive shaping pressures exceeding 1,000 kg usually result in formation of tablets of longer oral cavity dissolution time. In some cases, however, tablets with practically acceptable strength are obtained from an appropriate combination of two or more the pharmaceutical additives, even when the compressive shaping pressure is lower than 50 kg. Also, in some cases tablets with shorter oral cavity dissolution time may be obtained from an appropriate combination of two or more the pharmaceutical additives, even when the compressive shaping pressure exceeds 1,000 kg. Fast soluble tablets produced under a compressive shaping pressure out of the range of 50 - 1,000 kg are therefore included in the scope of the present invention.

Tablets whose tensile strength exceeds 5 kg/cm^2 are practically applicable. In some cases, however, tablets with even lower tensile strength are practically applicable if they are packaged in suitable forms.

The mechanical strength of the fast soluble tablet relating to the present invention is retained mainly by the crosslinking force of the pharmaceutical additive rapidly soluble in water.

Conventional tablets are produced under compressive shaping pressures of about 500 - 3,000 kg.

When a sugar alcohol is applied in the present invention, e.g., xylitol is used alone, it is preferable that the compressive shaping pressure is about 50 - 300 kg. Lower compressive shaping pressures make tablet shaping difficult. Higher compressive shaping pressures result in formation of practically unapplicable tablets of insufficient tensile strength (see Figure 1).

When xylitol alone is used as a sugar alcohol, compressive shaping pressures exceeding 300 kg result in formation of tablets with decreased tensile strength and increased oral cavity dissolution time. When xylitol is used in a mixture with lactose, mannitol or the like, tablets with sufficiently high tensile strength and short oral cavity dissolution time can be obtained even when the compressive shaping pressure exceeds 300 kg.

For example, when xylitol is used in combination with lactose, tablets with shorter oral cavity dissolution time and sufficient tensile strength can be obtained by mixing them in a ratio of, for example, 8:2 (see Figure 2).

For example, when xylitol is used in combination with mannitol, tablets with shorter oral cavity dissolution time and sufficient tensile strength can be obtained by mixing them in a ratio of, for example, 8:2 (see Figure 3).

As mentioned above, when xylitol is used in a mixture with lactose or mannitol, better results are obtained than those obtained with xylitol alone. These results, however, have not been expected from the results with mannitol alone or lactose alone. This is because using mannitol alone or lactose alone results in considerably increased oral cavity dissolution time as well as increased tensile strength when the compressive shaping pressure exceeds 300 kg (see Figure 4).

The fast soluble tablet relating to the present invention is characterized by rapid dissolution in the oral cavity. For example, when it is intended to incorporate a drug which may cause a problem, if used as such, e.g., a drug which has a high bitterness, a masking treatment such as microcapsulation or crystal surface coating is performed as appropriate, after which the drug is incorporated in the fast soluble tablet of the present invention, result in elimination of such problem.

The kneaded mixture of a drug and a pharmaceutical additive rapidly soluble in water is usually prepared by mixing the pharmaceutical additive rapidly soluble in water and the appropriately treated drug, adding and uniformly dispersing water, a binder solution or a saturated sugar solution, and kneading. The amount of water added is preferably about 1 - 10% by weight, most preferably about 3% by weight, in the tablet composition before compressive shaping. Excess water results in dissolution of sugar alcohol or sugar, or decreased shape retention, which in turn adversely affect the compressive shaping that follows and make it difficult to dry the shaped product. Insufficient water results in tableting failures such as cracking at shaping, thus hampering preferred embodiment. The shaped tablet, even if obtained, lacks

mechanical strength, and is fragile. The water added is preferably purified water, for instance.

Compressive shaping can be achieved, irrespective of the form of the kneaded mixture, whether particulate, granular, soft lumpy or the like, as long as the kneaded mixture of the drug and the pharmaceutical additive rapidly soluble in water is wet. Compressive shaping machines which can be used include ordinary tableting machines, automatic compressive shaping machines for Japanese cakes and lump sugar machines.

The fast soluble tablet relating to the present invention can be produced more simply and in larger amounts, in comparison with the above-described tableting method using freeze-drying technique, because they can be produced by a modification of the conventional tableting method based on wet granulation compression, as stated above.

In the present invention, to further improve the physical properties of the preparation, known binders may be added in the process of the kneading operation. Although the binder for the present invention is not subject to limitation, preference is given to substances of relatively high dissolution rate. Such binders include polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) and the like. Acacia etc. may also be incorporated as appropriate.

The binder for the present invention may be contained at 0.1 to several percent by weight, preferably about 0.5 - 1% by weight, in the tablet composition before compressive shaping.

The fast soluble tablet relating to the present invention may be glazed by steam exposure for one to several seconds after compressive shaping and drying, to smooth the tablet surface for good appearance and prevent abrasion of the tablet surface.

Any drug is applicable to the fast soluble tablet relating to the present invention, as long as it is orally administered. Such drugs include the following:

1. Antipyretic analgesic anti-inflammatory agents

Indomethacin, aspirin, diclofenac sodium, ketoprofen, ibuprofen, mefenamic acid, dexamethasone, dexamethasone sodium sulfate, hydrocortisone, prednisolone, azulene, phenacetin, isopropylantipyrin, acetaminophen, benzydamine hydrochloride, phenylbutazone, flufenamic acid, mefenamic acid, sodium salicylate, choline salicylate, sasapyrine, clofezone, etodolac.

2. Antiulcer agents

Sulpiride, cetraxate hydrochloride, gefarnate, irsogladine maleate, cimetidine, unitidine hydrochloride, famotidine, nizatidine, roxatidine acetate hydrochloride.

3. Coronary vasodilators

Nifedipine, isosorbide dinitrate, diltiazem hydrochloride, trapidil, dipyridamole, dilazep dihydrochloride, methyl 2,6-dimethyl-4-(2-nitrophenyl)-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylate, verapamil, nicardipine, nicardipine hydrochloride, verapamil hydrochloride.

4. Peripheral vasodilators

Ifenprodil tartrate, cinepazide maleate, cyclandelate, cinnarizine, pentoxyfyline.

5. Antibiotics

Ampicillin, amoxicillin, cefalexin, erythromycin ethylsuccinate, bacampicillin hydrochloride, minocycline hydrochloride, chloramphenicol, tetracycline, erythromycin.

6. Synthetic antibacterial agents

Nalidixic acid, piromidic acid, pipemidic acid trihydrate, enoxacin, cinoxacin, ofloxacin, norfloxacin, ciprofloxacin hydrochloride, sulfamethoxazole trimethoprim, 6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-1-piperazinyl]-4-oxo-4H[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid.

7. Antispasmodics

Propantheline bromide, atropine sulfate, oxopium bromide, timebidium bromide, butylscopolamine bromide, trospium chloride, butropium bromide, N-methylscopolamine methylsulfate, methyloctatropine bromide, butropium bromide.

9. Antitussive, anti-asthmatic agents

Theophylline, aminophylline, methylephedrine hydrochloride, procaterol hydrochloride, trimetoxinol hydrochloride, codeine phosphate, sodium cromoglicate, tranilast, dextromethorphane hydrobromide, dimemorfan phosphate, clobutinol hydrochloride, fominoben hydrochloride, benproperine phosphate, dimemorfan phosphate, tipepidine hibenzate, eprazinone hydrochloride, clofedanol hydrochloride, ephedrine hydrochloride, noscapine, calbetapentane citrate, oxeladin tannate, isoaminile citrate, eprazinone hydrochloride.

10. Bronchodilators

Diprophylline, salbutamol sulfate, clorprenaline hydrochloride, formoterol fumarate, orciprenalin sulfate, pirbuterol hydrochloride, hexoprenaline sulfate, bitolterol mesylate, clenbuterol hydrochloride, terbutaline sulfate, mabuterol hydrochloride, fenoterol hydrobromide, methoxyphenamine hydrochloride.

11. Diuretics
Furosemide, acetazolamide, trichlormethiazide, thyclothiazide, hydrochlorothiazide, hydroflumethiazide, ethiazide, cyclopenthiazide, spironolactone, triamterene, fluorothiazide, piretamide, mefrumide, ethacrynic acid, azosemide, clofenamide.

12. Muscle relaxants
Chlorphenesin carbamate, tolperisone hydrochloride, eperisone hydrochloride, tizanidine hydrochloride, mephenesin, chlorozoxazone, phenprobamate, methocarbamol, chlormezanone, pridinol mesylate, afloqualone, baclofen, pridinol mesylate, dantrolene sodium.

13. Brain metabolism improvers
Meclofenoxate hydrochloride.

14. Minor tranquilizers
Oxazolam, diazepam, clotiazepam, metazepam, temazepam, fludiazepam, meprobamate, nitrazepam, chlordiasepoxide.

15. Major tranquilizers
Sulpirid, clocapramine hydrochloride, sodepine, chlorpromazinon, haloperidol.

16. β-blockers
Pindolol, propranolol hydrochloride, carteolol hydrochloride, metoprolol tartrate, labetalol hydrochloride, oxourenolol hydrochloride, acebutolol hydrochloride, buferelol hydrochloride, alprenolol hydrochloride, arotinolol hydrochloride, oxprenolol hydrochloride, nadolol, bucumolol hydrochloride, indenolol hydrochloride, timolol maleate, befunolol hydrochloride, carteolol hydrochloride, bupranolol hydrochloride.

17. Antiarrhythmic agents
Procainamide hydrochloride, disopyramide, ajimaline, quinidine sulfate, aprindine hydrochloride, propafenone hydrochloride, mexiletine hydrochloride.

18. Gout suppressants
Allopurinol, probenecid, colchicine, sulfinpyrazone, benzbromarone, bucolome.

19. Anticoagulants
Ticlopidine hydrochloride, dicumarol, fulfarin potassium.

20. Antiepileptic agents
Phenytoin, sodium valproate, metharbital, carbamazepine.

21. Antihistaminics
Chlorpheniramine maleate, clemastin fumarate, mequitazine, alimemazine tartrate, cycloheptazine hydrochloride.

22. Antiemetics
Difenidol hydrochloride, metoclopramide, domperidone, betahistine mesylate, trimebutine maleate.

23. Hypotensives
Dimethylaminoethyl reserpilinate dihydrochloride, rescinnamine, methyldopa, prazosin hydrochloride, bunazosin hydrochloride, clonidine hydrochloride, budralazine, urapidin.

24. Sympathomimetic agents
Dihydroergotamine mesylate, isoproterenol hydrochloride, etilefrine hydrochloride.

25. Expectorants
Bromhexine hydrochloride, carbocysteine, ethyl cysteine hydrochloride, methyl cysteine hydrochloride.

26. Oral antidiabetic agents
Glibenclamide, tolbutamide, glymidine sodium.

27. Circulatory agents
Ubidecarenone, ATP-2Na.

28. Iron preparations
Ferrous sulfate, dried ferrous sulfate.

29. Vitamins
Vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, folic acid.

30. Pollakiuria remedies
Flavoxate hydrochloride, oxybutynin hydrochloride, terodiline hydrochloride, 4-diethylamino-1,1-dimethyl-2-butynyl (±)-α-cyclohexyl-α-phenylglycolate hydrochloride monohydrate.

31. Angiotensin-converting enzyme inhibitors
Enalapril maleate, alacepril, delapril hydrochloride.

EFFECTS OF THE INVENTION

The fast soluble tablet relating to the present invention has the following effects:
(1) Offers improved compliance, including safe administration to the aged, children, infants and patients weak in swallowing ability.
(2) Free of the risk of suffocation due to a physical obstruction when swallowed, thus offering improved safety.
(3) Safely administrable to patients on water intake restriction.
(4) Easily portable and suitable for transportation by patients.
(5) Free of the need of weighing, an essential drawback in liquids etc.
(6) Drug retention at high concentrations in tablets allows application to drugs that must be administered at high doses.
(7) Can be industrially produced more simply, more efficiently and in larger amounts, in comparison with tableting based on freeze-drying.

BEST MODES FOR CARRYING OUT THE INVENTION

The present invention is hereinafter illustrated in more detail by means of the following examples.

Example 1

To 60 g of xylitol, 2 ml of purified water was added, followed by kneading in a mortar. 1 g of the kneaded mixture was subjected to compressive shaping at a compression force of 100 - 700 kg and a compression rate of 20 mm/min, using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation), to yield tablets of 13 mm diameter. The resulting tablets were dried at 50 °C for 2 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 2

48 g of xylitol and 12 g of lactose were uniformly mixed in a mortar, followed by kneading with 2 ml of purified water added. 1 g of the kneaded mixture was subjected to compressive shaping at a compression force of 100 - 700 kg and a compression rate of 20 mm/min, using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation), to yield tablets of 13 mm diameter. The resulting tablets were dried at 50 °C for 2 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 3

48 g of xylitol and 12 g of mannitol were uniformly mixed in a mortar, followed by kneading with 2 ml of purified water added. 1 g of the kneaded mixture was subjected to compressive shaping at a compression force of 100 - 700 kg and a compression rate of 20 mm/min, using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation), to yield tablets of 13 mm diameter. The resulting tablets were dried at 50 °C for 2 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 4

60 g of mannitol was placed in a mortar and kneaded with 2 ml of purified water. 1 g of the kneaded mixture was subjected to compressive shaping at a compression force of 100 - 700 kg and a compression rate of 20 mm/min, using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation), to yield tablets of 13 mm diameter. The resulting tablets were dried at 50 °C for 2 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 5

308 g of xylitol, 77 g of mannitol, 12.5 g of diclofenac sodium and 2.5 g of polyvinylpyrrolidone were mixed in a kneader (KM-1.5, produced by Kikusui Seisakusho, Ltd.) for 10 minutes, followed by kneading with 12 ml of purified water added. The resulting mixture was applied to a feather mill (FM-1, produced by Hosokawa Micron Corp.) equipped with a screen of 12 mm pores, to uniformize particle size. The resulting granules were subjected to compressive shaping at a compression force of 200 kg, using a tableting machine (Clean Press Correct 12HUK, produced by Kikusui Seisakusho, Ltd.) equipped with a forced mechanical stirrer, to yield tablets of 10.5 mm diameter weighing 800 mg each. The shaped tablets were then dried at 50 °C for 3 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 6

3 g of polyvinylpyrrolidone, 100 g of lactose and 3 g of oxybutynin hydrochloride were mixed in a micro-type through-vision mixer (W-8, produced by Tsutsui Rikagaku Kiki) for 8 minutes. 106 g of this mixture and 394 g of xylitol were mixed in a kneader (KM-1.5, produced by Kikusui Seisakusho, Ltd.) for 10 minutes, followed by kneading with 15 ml of purified water added. The resulting mixture was applied to a feather mill (FM-1, produced by Hosokawa Micron Corp.) equipped with a screen of 12 mm pores, to uniformize particle size. The resulting granules were subjected to compressive shaping at a compression force of 150 kg, using a tableting machine (Clean Press Correct 12HUK, produced by Kikusui Seisakusho, Ltd.) equipped with a forced mechanical stirrer, to yield tablets of 9 mm diameter weighing 500 mg each. The shaped tablets were then dried at 55 °C for 3 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 7

2.5 g of acacia powder, 146 g of mannitol and 10 g of nifedipine were mixed in a micro-type through-vision mixer (W-8, produced by Tsutsui Rikagaku Kiki) for 8 minutes. 158.5 g of this mixture and 341.5 g of xylitol were mixed in a kneader (KM-1.5, produced by Kikusui Seisakusho, Ltd.) for 10 minutes, followed by kneading with 14 ml of purified water added. The resulting mixture was applied to a feather mill (FM-1, produced by Hosokawa Micron Corp.) equipped with a screen of 12 mm pores, to uniformize particle size. The resulting granules were subjected to compressive shaping at a compression force of 220 kg, using a rotary tableting machine (RT-F-9, produced by Kikusui Seisakusho, Ltd.), to yield tablets of 15 mm diameter weighing 1,000 mg each. The shaped tablets were then dried at 55 °C for 3 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 8

1.5 g of polyvinylpyrrolidone, 412.5 g of xylitol, 111 g of lactose and 125 g of cefalexin were mixed in a kneader (KM-1.5, produced by Kikusui Seisakusho, Ltd.) for 10 minutes, followed by kneading with 20 ml of purified water added. The resulting mixture was applied to a feather mill (FM-1, produced by Hosokawa Micron Corp.) equipped with a screen of 12 mm pores, to uniformize particle size. The resulting granules were subjected to compressive shaping at a compression force of 180 kg, using a rotary tableting machine (RT-F-9, produced by Kikusui Seisakusho, Ltd.), to yield tablets of 15 mm diameter weighing 1,300 mg each. The shaped tablets were then dried at 55 °C for 3 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Comparative Example 1

300 g of xylitol was passed through a 32-mesh sieve. 1 g of the powder was subjected to compressive shaping at a compression force of 50 - 1,000 kg and a compression rate of 20 mm/min, using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation), to yield tablets of 13 mm diameter for comparative testing.

Comparative Example 2

300 g of mannitol was passed through a 32-mesh sieve. 1 g of the powder was subjected to compressive shaping at a compression force of 100 - 700 kg and a compression rate of 20 mm/min, using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation), to yield tablets of 13 mm diameter for comparative testing.

Test Example 1

For the inventive fast soluble tablets of Example 1, the tablets of Comparative Example 1, and the undried tablets of Example 1, tensile strength and oral cavity dissolution time were measured. Tensile strength was measured using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation) equipped with a 100 KGF load cell, at a compression rate of 20 mm/min, with a full scale of 10 - 20 KGF. The point at which the load reduction rate for 1 second lowerd to 50% of the full scale was taken as the breaking point. On the basis of breaking point data, the tensile strength of each tablet preparation was calculated as the mean of 5 tablets using the following equation:

$$\tau = 2P/\pi DT$$

τ : Tensile strength (kg/cm^2)
P: Hardness (kg)
D: Tablet diameter (cm)
T: Tablet thickness (cm)

Oral cavity dissolution time was measured as the mean of 5 subjects. Each tablet was kept unbitten in the mouth, and the time to tablet mass dissolution and disappearance was measured. The results are given in Figure 1.

From Figure 1, it is seen that the fast soluble tablet of the present invention had excellent properties for a fast soluble tablet, having a tensile strength exceeding 3 kg/cm^2 and an oral cavity dissolution time within 30 second when it was prepared under a compression force of 50 - 300 kg. As for the undried tablets and the tablets obtained by dry tableting, tensile strength was lower than 3 kg/cm^2 when they were prepared under a compression force of 50 - 1,000 kg; they were not practically applicable.

Test Example 2

For the inventive fast soluble tablets of Example 2, tensile strength and oral cavity dissolution time were measured in the same manner as in Test Example 1. The results are given in Figure 2.

From Figure 2, it is seen that the fast soluble tablet of the present invention has excellent properties for a fast soluble tablet, having a tensile strength exceeding 8 kg/cm^2 and an oral cavity dissolution time within 1 minute over the range of compression forces measured.

Test Example 3

For the inventive fast soluble tablets of Example 3, tensile strength and oral cavity dissolution time were measured in the same manner as in Test Example 1. The results are given in Figure 3.

From Figure 3, it is seen that the fast soluble tablet of the present invention had excellent properties for a fast soluble tablet, having a tensile strength exceeding 7 kg/cm^2 and an oral cavity dissolution time within 40 seconds over the range of compression forces measured.

Test Example 4

For the inventive fast soluble tablets of Example 4, the tablets of Comparative Example 2 and the undried tablets of Example 4, tensile strength and oral cavity dissolution time were measured in the same manner as in Test Example 1. The results are given in Figure 4.

From Figure 4, it is seen that the fast soluble tablet of the present invention were practically applicable, having much higher tensile strength, in comparison with the undried tablets and the tablets obtained by dry tableting.

Test Example 5

For the inventive fast soluble tablets of Examples 5 through 8, tensile strength, oral cavity dissolution time, disintegration time and degree of wear were measured. Tensile strength and oral cavity dissolution time were measured in the same manner as in Test Example 1. Disintegration time was measured by the method using water specified in the Pharmacopoeia of Japan. Friability was measured on one tablet for each preparation, using a friabilator. The results are given in Table 1.

Table 1

	Example 5	Example 6	Example 7	Example 8
Tensile strength (kg/cm^2)	9.1	7.5	12.2	8.5
Dissolution time (in oral cavity, seconds)	15	15	18	25
Disintegration time (seconds)	12	12	15	20
Friability (%) (in 3 minutes)	0.3	0.1	0.2	0.3
Remarks	*Good appearance *Dissolved rapidly in the oral cavity. *Easily swallowable.	*Good appearance *Dissolved rapidly in the oral cavity. *Easily swallowable.	*Good appearance *Dissolved rapidly in the oral cavity. *Easily swallowable.	*Good appearance *Dissolved rapidly in the oral cavity. *Easily swallowable.

From Table 1, it is seen that the fast soluble tablets of the present invention had excellent properties for a fast soluble tablet, having a tensile strength exceeding 7 kg/cm^2 and an oral cavity dissolution time within 30 seconds.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the relations between tensile strength, and oral cavity dissolution time and compression force for each of the inventive fast soluble tablets of Example 1, the tablets of Comparative Example 1, and the undried tablets of Example 1.

The abscissa indicates compression force; the left ordinate indicates tensile strength (kg/cm^2); the right ordinate indicates oral cavity dissolution time (min).

In Figure, the symbols denote the following:

- ■ - : Tensile strength of the inventive fast soluble tablets of Example 1
- □ - : Oral cavity dissolution time of the inventive fast soluble tablets of Example 1
- ▲ - : Tensile strength of the undried tablets of Example 1
- ● - : Tensile strength of the tablets of Comparative Example 1

Figure 2 shows the relations between tensile strength, and oral cavity dissolution time and compression force for the inventive fast soluble tablets of Example 2.

The abscissa indicates compression force; the left ordinate indicates tensile strength (kg/cm^2); the right ordinate indicates oral cavity dissolution time (min).

In Figure, the symbols denote the following:

- ■ - : Tensile strength of the inventive fast soluble tablets of Example 2
- □ - : Oral cavity dissolution time of the inventive fast soluble tablets of Example 2

Figure 3 shows the relations between tensile strength, and oral cavity dissolution time and compression force for the inventive fast soluble tablets of Example 3.

The abscissa indicates compression force; the left ordinate indicates tensile strength (kg/cm^2); the right ordinate indicates oral cavity dissolution time (min).

In Figure, the symbols denote the following:

- ■ - : Tensile strength of the inventive fast soluble tablets of Example 2

- □ - : Oral cavity dissolution time of the inventive fast soluble tablets of Example 2

Figure 4 shows the relations between tensile strength, and oral cavity dissolution time and compression force for each of the inventive fast soluble tablets of Example 4, the tablets of Comparative Example 1, and the undried tablets of Example 1.

The abscissa indicates compression force; the left ordinate indicates tensile strength (kg/cm^2); the right ordinate indicates oral cavity dissolution time (min).

In Figure, the symbols denote the following:

- ■ - : Tensile strength of the inventive fast soluble tablets of Example 4
- □ - : Oral cavity dissolution time of the inventive fast soluble tablets of Example 4
- ▲ - : Tensile strength of the undried tablets of Example 4
- ● - : Tensile strength of the tablets of Comparative Example 2

Claims

1. A fast soluble tablet which comprises two features: ① the tablet base component is a pharmaceutical additive rapidly soluble in water, and ② a kneaded mixture of a drug and a pharmaceutical additive rapidly soluble in water is subjected to compressive shaping prior to drying when compressive shaped in the process for preparing drug-containing tablets by wet granulation.

2. The fast soluble tablet of claim 1, wherein said pharmaceutical additive rapidly soluble in water is a sugar alcohol or a sugar.

3. The fast soluble tablet of claim 2, wherein said sugar alcohol is xylitol.

4. The fast soluble tablet of claim 3, wherein said tablet is prepared at 50 - 300 Kg of the compressive shaping pressure.

5. The fast soluble tablet of claim 1, wherein said pharmaceutical additive rapidly soluble in water is a mixture of xylitol and lactose.

6. The fast soluble tablet of claim 1, wherein said pharmaceutical additive rapidly soluble in water is a mixture of xylitol and mannitol.

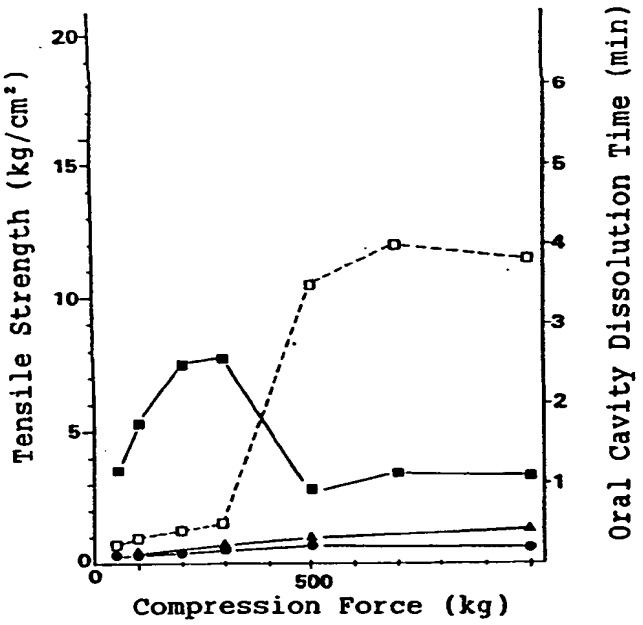
Tensile Strength (kg/cm²)
Oral Cavity Dissolution Time (min)
Compression Force (kg)
0
5
10
15
20
1
2
3
4
5
6
500

Fig. 1

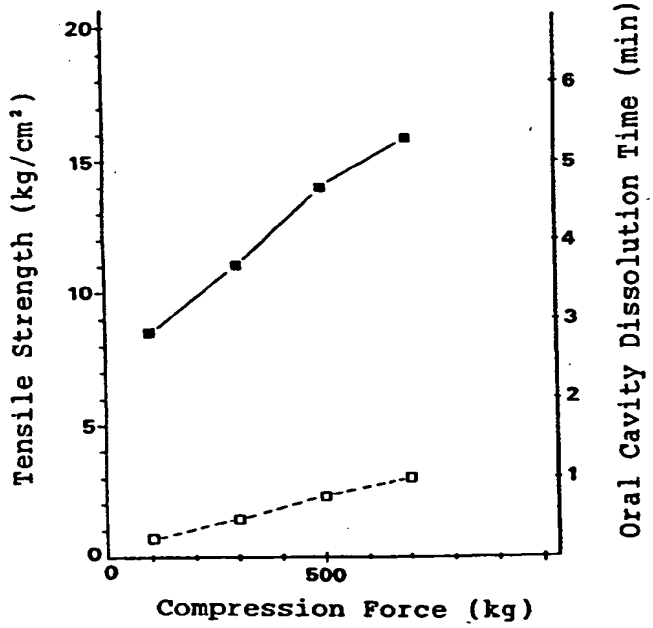
Tensile Strength (kg/cm²)
Oral Cavity Dissolution Time (min)
Compression Force (kg)
0
5
10
15
20
1
2
3
4
5
6
500

Fig. 2

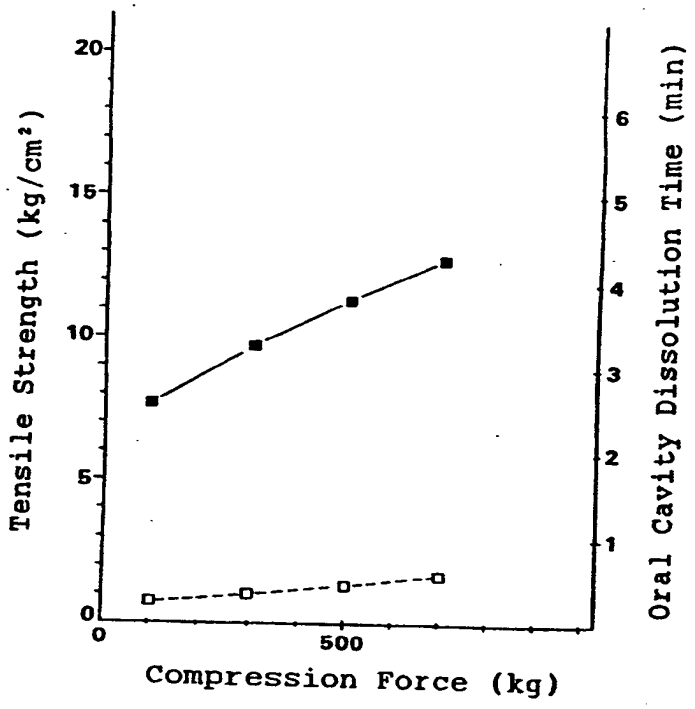
Tensile Strength (kg/cm²)
Oral Cavity Dissolution Time (min)
Compression Force (kg)
0
5
10
15
20
1
2
3
4
5
6
500

Fig. 3

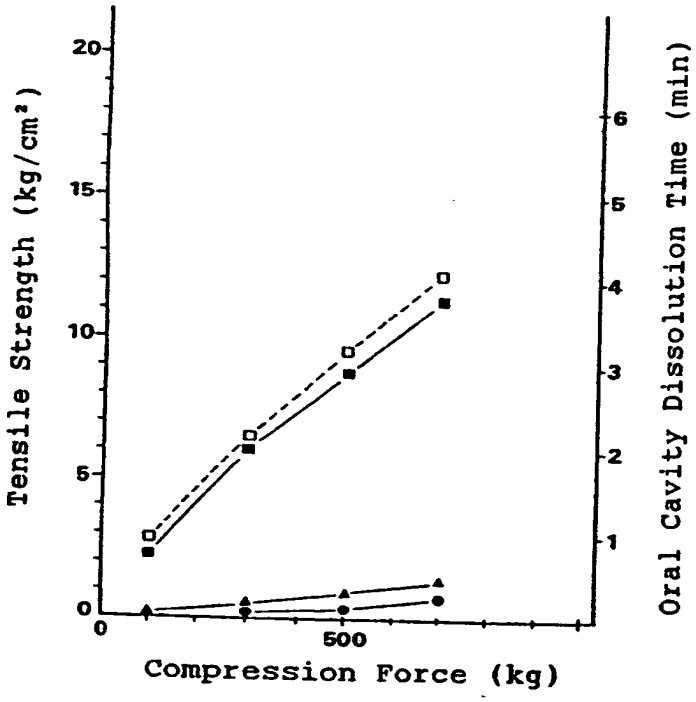
Tensile Strength (kg/cm²)
Oral Cavity Dissolution Time (min)
Compression Force (kg)
0
5
10
15
20
1
2
3
4
5
6
500

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/00192

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^5 A61K9/20, A61K47/10, 47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl^5 A61K9/20, A61K47/06-47/26, 47/36-47/40

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 60-255736 (Bayer AG.), December 17, 1985 (17. 12. 85), & DE, A1, 3419129 & EP, A2, 164587	1-6
A	JP, A, 61-205208 (Yamanouchi Pharmaceutical Co., Ltd.), September 11, 1986 (11. 09. 86), (Family: none)	1-6
A	JP, A, 53-44618 (Takeda Chemical Industries, Ltd.), April 21, 1978 (21. 04. 78), (Family: none)	1-6

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
May 20, 1993 (20. 05. 93)	June 8, 1993 (08. 06. 93)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)